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Radiological tips on pulmonary sarcoidosis imaging: The invisible side of iceberg's

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Abstract
Aim: In our study, we aimed to investigate computed tomography (CT) findings in lung sarcoidosis in the light of different studies in the literature.
Material and Methods: Between January 2018 and September 2021, all thorax computed tomography reports were retrospectively scanned in our clinic. The imaging characteristics of 60 patients were examined, whose sarcoidosis findings were defined and diagnosed as sarcoidosis.
Results: In the staging of sarcoidosis, 15 (25%) patients were stage I, 42 (70%) patients were stage II, 2 (3.3%) patients were stage III, and 1 (1.7%) patient were stage IV. All our patients with lymph nodes (57 (Stage I and II)) were observed symmetrically. Calcification was present in 5 (8.7%) patients with lymph nodes, and 52 (91.3%) did not have calcification or necrosis. In 6 patients, lymph nodes other than the mediastinum were detected in the axilla and abdomen. When the lymph nodes seen in the axilla and abdomen other than the mediastinum were examined, it was found that the lymph nodes in the mediastinum were larger. In addition, it was determined that the fatty hilus of these lymph nodes, which were detected outside of the mediastinum, could not be distinguished. No accompanying cavitary lesion was observed in any of the lung parenchymal findings. In addition, in 16 (26.6%) patients with parenchymal results, scattered nodules smaller than 1 cm were observed without any other parenchymal conclusion. An increase in peribronchovascular cuffing and peribronchovascular nodular appearances were observed in 20 (33.3%) patients.
Discussion: Sarcoidosis is a disease that should always be considered in the differential diagnosis of atypical parenchymal findings in the lung or mediastinal lymph nodes.

Keywords
Sarcoidosis, Lung, Tomography, Lymph Nodes

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Introduction

Sarcoidosis is a systemic disease of unknown etiology characterized by histologically non-caseating granulomas that occur in any organ, with more involvement in the intrathoracic lymph nodes and lung [1]. When the disease occurs, mediastinal lymph nodes and lungs are frequently affected. Therefore, a biopsy of the mediastinal lymph nodes is recommended in the definitive diagnosis and treatment management of the disease [2]. Sarcoidosis is more common between the ages of 25-45 and can appear in younger or older generations. The condition is slightly more common in women [3,4].

Mediastinal lymphadenopathy in sarcoidosis is symmetrical, and the resulting lymphadenopathies do not show a mass effect on adjacent vascular structures. In lung parenchymal findings, micronodules, macro nodules, ground glass opacities, reticulations, and fibrosis can be seen [5]. The lungs, the most frequently affected organ in pulmonary sarcoidosis, can be classified into four stages according to the state of the disease. There is lymphadenopathy in stage I, lymphadenopathy and parenchymal findings in stage II, parenchymal findings in stage III, and parenchymal fibrosis in stage IV [6]. Although the optimal treatment method for sarcoidosis has not been specified, corticosteroid therapy has been used for a long time in patients with severe symptoms or patients with severe extrapulmonary findings. Spontaneous remission was detected in two-thirds of patients, even if they did not receive treatment [7].

Sarcoidosis can be indistinguishable from many diseases clinically and radiologically. However, since sarcoidosis can progress with atypical findings such as mediastinal asymmetric and peripheral lymphadenopathy, differential diagnosis with lung cancer, lymphoma, tuberculosis, and other granulomatous diseases becomes difficult. Furthermore, atypical lung parenchymal findings can be indistinguishable from bronchiolitis, lymphangitic carcinomatosis, and some interstitial pneumonia [4]. Therefore, in our study, we aimed to investigate a wide range of computed tomography (CT) findings in pulmonary sarcoidosis, which is overlooked in the differential diagnosis, in light of different studies in the literature.

Material and Methods

Patients: This single-center retrospective observational study was initiated with the approval of the medical faculty's clinical research ethics committee with ethical approval number 2021/10-12. All thorax computed tomography (CT) reports in our clinic between January 2018 and September 2021 were scanned retrospectively. PACS (picture archiving and communication system) examined two hundred ten patients with sarcoidosis findings. Among these patients, patients with a histopathological diagnosis or typical tomography findings who responded to treatment and whose clinical-radiological follow-ups were performed in our center were included in the study. In addition, 89 patients with suspicious sarcoidosis, 27 patients who were not followed up in our hospital, 32 patients without histopathological diagnosis or questionable response to treatment, and two patients with apparent artifacts were excluded from the study. The study was performed with 60 patients who met the inclusion criteria.

Acquisition and evaluation of images: All tomography examinations were performed using a 16-slice (Siemens Medical Systems, Germany) CT device, according to the routine thorax CT protocol, with the patients lying in the supine position and holding the breath after deep inspiration with or without intravenous contrast material, thorax CT scans were performed from the lung apex to the lowest level of the hemidiaphragm. In contrast-enhanced examinations, patients were injected with 1-1.5 mL/kg non-ionizing intravenous contrast agent iohexol (Amersham Health, Ireland) or iopromide (Schering, Germany) at a rate of 2-3 mL/second through the forearm vein via an automatic injector. Images were obtained with an average of 120 kV, 200 practical mA, 16x1.5 mm collimation, 3 mm section thickness, and 512x512 matrix parameters. The images were evaluated in standard mediastinal and parenchymal window settings by two radiologists with 14 and 7 years of experience in thoracic radiology, with consensus. Regardless of the clinical data of the patients, the images were examined. The stage of sarcoidosis, symmetric/asymmetric lymph nodes involved, presence of necrosis or calcification in lymph nodes, presence of accompanying cavitary mass in the lung, presence of accompanying pneumonia, isolated nodular involvement in parenchymal findings, peribronchovascular nodular appearance, and lower-middle-upper zone intensity parenchymal involvement were noted. In addition, the presence of accompanying organomegaly and extrathoracic participation in the upper abdominal images were examined. Then, the age, gender, biopsy result, and concomitant solid-hematological malignancy were noted. Patients with histopathological examination were accepted as sarcoidosis according to the pathology result. Also, patients with typical radiological findings who responded to treatment and whose other differential diagnoses were excluded were taken as sarcoidosis. The characteristic radiological findings of sarcoidosis were accepted as bilateral symmetric hilar lymphadenopathy, accompanied by parenchymal findings [4]. Patients with pulmonary sarcoidosis involvement and radiological extrathoracic findings were considered to have sarcoidosis involvement.

Statistical analysis and examination of findings: The features determined in the tomography were recorded in an Excel file, and the relevant results were evaluated in the statistics program if necessary. Descriptive statistics for the variables studied were presented as mean, standard deviation, minimum and maximum values. The SPSS (ver: 20) statistical program was used for all statistical calculations.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 60 patients, 43 females (71.6%) and 17 males (28.4) with a mean age of 49.26 ± 11.30 (20-70 years), were included in the study.

The diagnosis of sarcoidosis was made by biopsy in 37 patients and by having typical radiological findings in 23 patients or responding to treatment.

In the staging of sarcoidosis, 15 (25%) patients were stage I (Figure 1), 42 (70%) patients were stage II (Figure 2), 2 (3.3%) patients were stage III, and 1 (1.7%) was stage IV. In all our patients with lymph nodes, 57 (Stage I and Stage II)

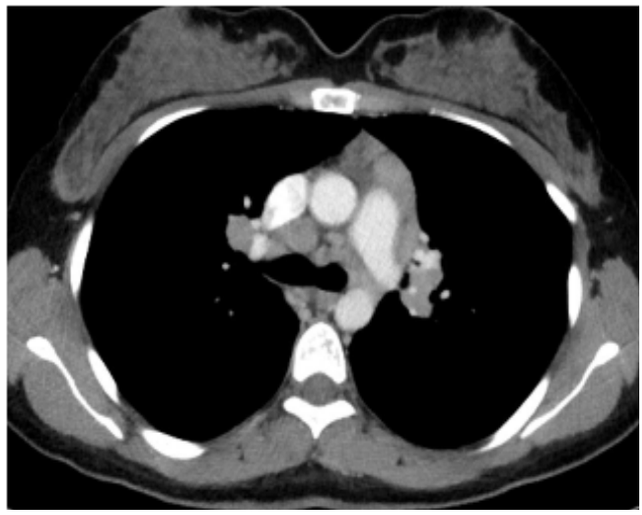

Figure 1. Stage 1 sarcoidosis. Symmetrical lymphadenopathy in both hilar regions. No lung parenchymal findings.

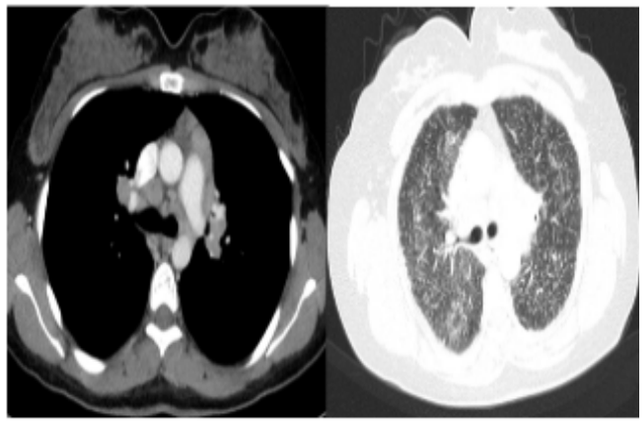

Figure 2. Stage 2 sarcoidosis. Symmetrical lymphadenopathy in both hilar regions. Some ground-glass fields accompany peribronchovascular millimetric nodular infiltrates in the lung parenchyma.

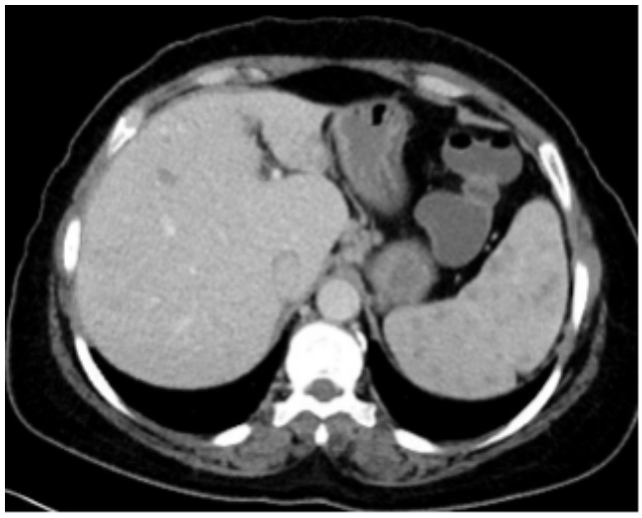

Figure 3. Abdominal sarcoidosis. A 48-year-old female patient was diagnosed with thoracic sarcoidosis, millimetric nodular non-enhancing hypodense lesions in the spleen and liver.

Table 1. Sarcoidosis staging and definitional features of lymph nodes.

Sarcoidosis stage			Lymph nodes distribution		Lymph nodes features	
			Symmetrical	Asymmetric	Calcification	Necrosis
Stage 1	n	15	15	0	3	0
	%	25	100	0	5,2	0
Stage 2	n	42	42	0	2	0
	%	70	100	0	3,5	0
Stage 3	n	2				
	%	3,3				
Stage 4	n	1				
	%	1,7				

Table 2. Definitional features of sarcoidosis lung parenchymal manifestations.

Nodules smaller than 1 cm	n	16
	%	26,6
Increased peribronchovascular cuffing Peribronchovascular nodular appearance	n	20
	%	33,3
Other parenchymal findings (Consolidation, ground glass, atelectasis)	n	9
	%	20

lymph nodes were observed symmetrically. Calcification was present in 5 (8.7%) patients with lymph nodes, and 52 (91.3%) did not have calcification or necrosis (Table 1). Axillary and abdominal lymph nodes were detected in 6 patients, except for the mediastinum. When the lymph nodes seen in the axilla and abdomen other than the mediastinum were examined, it was found that the lymph nodes in the mediastinum were larger. In addition, it was determined that the fatty hilus of these lymph nodes, which were detected outside of the mediastinum, could not be distinguished.

No accompanying cavitary lesion was observed in any of the lung parenchymal findings. In addition, in 16 (26.6%) patients with parenchymal results, scattered nodules smaller than 1 cm were observed without any other parenchymal conclusion. An increase in peribronchovascular cuffing and peribronchovascular nodular appearances were observed in 20 (33.3%) patients. Other findings (consolidation, ground glass, atelectasis) were present in 9 patients (Table 2).

The involvement was classified as an upper, middle, and lower zone in 45 patients with parenchymal involvement. In in 22 (48.8%) patients, in all zones, in 12 (26.6%) patients, upper and middle zone involvements, and in 11 (24.6%) patients, middle and lower zone involvements were detected. The dominant findings were in patients with all-zone involvement in the upper zone.

When accompanying organomegaly was examined, only hepatomegaly was found in 6 patients, and hepatomegaly and splenomegaly were found in 6 patients. Only 1 of 6 patients with hepatomegaly had sarcoidosis involvement in the liver. Sarcoidosis involvement in the spleen or liver was detected in 5

of 6 patients with hepatomegaly and splenomegaly (Figure 3).

When extrathoracic involvement was examined, six patients had spleen or liver, 3 had cutaneous, and 1 had pituitary involvement.

When examined regarding solid or hematologic malignancies that may accompany sarcoidosis, two patients had breast cancer, and no hematological malignancy was detected in any of our patients.

Discussion

In this study, we retrospectively analyzed the radiological findings and demographic data of patients with sarcoidosis. A total of 60 patients, 43 females (71.6%) and 17 males (28.4) with a mean age of 49.26 ± 11.30 (20-70) years were included in the study. Most of the patients were stage II (70%) and later stage I (25%).

Although there is no significant epidemiological difference between men and women with sarcoidosis in the literature, 71.6% of the female patients in our study indicate that the disease is more common in women in our region [8]. Furthermore, considering the age range, it is observed that it is compatible with the literature, with an average age of 49 years [8].

Although there are different methods of diagnosing sarcoidosis, the diagnosis was made in our clinic with endoscopic biopsy, typical radiological findings, and evaluation of response to treatment [9]. When the stage of the diagnosed patients was examined, although results were found parallel to the literature, especially Stage II patients were detected more frequently in our clinic [9]. We think this is because patients apply to us later or prefer our hospital for their follow-up because we are an advanced center.

Although asymmetrical lymph nodes are not typical for sarcoidosis lymph nodes in the literature, it has been determined that they are rarely seen [10]. In our study, the lymph nodes were symmetrical in all of our patients, and we did not observe asymmetric lymph nodes in any of our patients. Studies of calcification in sarcoidosis lymph nodes have reported that it can be kept at 11%. In our research, calcification was observed in the lymph nodes in 8.7% of our patients, consistent with the literature [11]. Although rare, necrosis in the lymph nodes has been reported, and no necrosis was detected in our study patients [11].

In parenchymal lesions, mainly increased peribronchovascular cuffing and peribronchovascular nodular were observed. In addition, when we examined the parenchymal lesions, 26.6% of our patients had scattered nodules smaller than 1 cm in the parenchyma without any other finding. When the tomographies of the patients recorded in our system were examined, it was determined that they were previously diagnosed with sarcoidosis and that their lung parenchymal findings regressed. Nevertheless, sequelae in the form of nodules remained in their follow-up. In studies in the literature, it has been determined that there are only patients with accompanying nodules in the parenchyma [11].

Our patients had no solitary or cavitary mass regarding differential diagnosis in parenchymal findings regarding lung cancer that may accompany sarcoidosis. Lung cancer that may accompany sarcoidosis has been reported in the literature [12]. When the zonal distribution was examined, it was found that there was no significant difference in the involvement of the upper and lower zones, where diffuse involvement was predominant. The dominant findings were located in the upper zone in patients with all-zone participation. When the parenchymal involvement was examined, the upper zone involvement was slightly higher than the lower zones, but we did not observe a significant difference. Studies in the literature have reported that the upper zone can be involved two times more than the lower zone [11]. In addition, earlier literature studies have reported that the upper zone predominates [13].

The liver is the most frequently involved organ in abdominal sarcoidosis, although all abdominal organs can be affected. Liver involvement is sometimes not detected by tomography, and only hepatomegaly can be seen. Radiologically, it is observed as non-enhancing hypodense lesions varying from 1-3 mm to a few cm in the liver [5,14]. Isolated liver involvement in abdominal sarcoidosis is rare and is often accompanied by splenomegaly and spleen involvement. Folz et al. reported that in 75% of patients with liver involvement, spleen, and abdominal lymph nodes were involved. In our study, isolated hepatomegaly was observed in 6 patients, and only 1 (16.6%) of these patients had radiological involvement in the liver [15]. There was radiological sarcoidosis involvement in the spleen or liver in 5 (83.3%) of 6 patients with accompanying hepatomegaly and splenomegaly, and the findings were consistent with the detection of Folz et al. [15].

In studies on extrathoracic sarcoidosis in the literature, involvement rarely occurs and may present different clinical findings [4]. In our study, out of 60 patients, 6 (10%) patients had liver and spleen involvement, 3 (5%) patients had cutaneous involvement, and 1 (1.6%) had pituitary involvement.

Many studies indicate that hematological and solitary organ cancers may develop more in sarcoidosis patients [16,17]. Our analysis detected no hematological malignancy in any of our patients, but we saw breast cancer in 2 (3%) patients. When breast cancer was detected in one of the patients, sarcoidosis was not diagnosed. The other patient had advanced age and a family history of breast cancer.

Among the limitations of our study, it can be mentioned that study was retrospective; not all cases had a histopathological diagnosis, and some patients were not initially diagnosed in our hospital.

Conclusion

Sarcoidosis is a systemic disease that most commonly affects the lungs and can affect many other organs. In particular, the central and symmetrical distribution of lymph nodes, consideration of lung parenchymal findings and accompanying lymph nodes, and evaluation of attending extrathoracic results and pulmonary findings are essential in the differential diagnosis of thoracic sarcoidosis. Therefore, Sarcoidosis is a disease that should always be considered in the differential diagnosis of atypical parenchymal results in the lung or mediastinal lymph nodes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some

of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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